Electrocardiographic, Echocardiographic and Serum Biomarker Correlates of Chagas Heart Disease in Highly Endemic Communities of Rural Bolivia

**Dates of study:** Main study currently ongoing since May 2011. Our participation as collaborators in the study started in the month November 2011 (3.5 weeks). Future participation will complete a total of 8-10 weeks on site. We anticipate preliminary data analyses through March 2012 and final analyses by the end of 2012

**Location:** Camiri, Bolivia

**Foreign Institutions:** The project is currently carried out by Johns Hopkins University, the US Centers for Disease Control and Prevention and Hospital Universitario Japones (Bolivia).

**Brown Faculty Mentor:** Athena Poppas, MD. Associate Professor of Medicine. Director of the Echocardiography Laboratory at Rhode Island Hospital.

**Faculty Advisors:** Caryn Bern, MD MPH Centers for Disease Control and Prevention (CDC)
Robert Gilman, MD Johns Hopkins Bloomberg School of Public Health

**Objective and Specific Aims:** The overarching goals of our participation in the parent study is to measure the prevalence of electrocardiogram and echocardiographic abnormalities in participants who are seropositive for *Trypanosoma cruzi* and its correlation with serum biomarkers such as brain natriuretic peptide (BNP) and troponin levels. Our efforts will ultimately be instrumental in the identification of electrocardiographic and echocardiographic features that will determine subgroups of patients at a greater risk of progression of the disease. These patients could eventually be targeted for antiparasitic treatment and improved outcome.

**Specific Aim:** Determine the prevalence of electrocardiographic and echocardiographic features of Chagas cardiomyopathy and its correlation with clinical severity and serum biomarkers in highly endemic communities.

**Background and Significance:** Chagas is a neglected and preventable tropical disease that causes significant cardiac morbidity and mortality in underdeveloped nations. It represents a major public health problem and reason for disability in some Latin American countries. ¹ The disease is caused by the protozoan parasite *Trypanosoma cruzi*, and was discovered in 1909 by the Brazilian physician Carlos Chagas. ² It is transmitted by triatomine vectors to humans and domestic animals. There are an estimated 8-10 million people infected, and another 109 million at risk of infection in Latin America ³, ⁴

Most persons infected with T. cruzi pass through the acute phase with mild and often unrecognized symptoms ⁵. An estimated 20-30% of people without symptoms of disease will eventually progress over a period of years to decades to clinically evident disease. ⁶, ⁷ Chagas cardiomyopathy is characterized by a chronic inflammatory process in all chambers, damage to the conduction system, and often an apical aneurysm. Ongoing inflammation eventually leads to collagen deposition and fibrosis of cardiac muscle and conduction fibers. The earliest signs of
Chagas heart disease (CHD) are conduction system abnormalities, classically manifested with right bundle branch block, left anterior hemiblock, and premature ventricular contractions. The late form of the disease, include dilated cardiomyopathy, congestive heart failure, ventricular arrhythmias, sinus node dysfunction, high degree atrioventricular block and the formation of left ventricular thrombi. The advanced form of the disease, often cause sudden cardiac death, in a range as high as 29% to 37%.

Traditional echocardiographic measures of systolic and diastolic function in patients with CHD are non-specific and can be found in other types of cardiomyopathies. The determination of an impaired left ventricular systolic function in CHD has been linked to decreased survival, but the detection of subclinical or early markers of chagas cardiomyopathy in the indeterminate form remains a challenge. In Chagas cardiomyopathy, the early detection of minor segmental regional wall motion abnormalities has been associated with worsening systolic function. Nonetheless, the visual assessment of minor wall motion abnormalities and systolic function estimates with conventional echocardiographic techniques vary greatly with reader training, are semi-quantitative and remain highly subjective. The advent of tissue Doppler imaging (TDI) has allowed the detection of diastolic and systolic dysfunction with greater sensitivity and specificity. In addition to traditional echocardiographic parameters and diastolic dysfunction by TDI, we will measure myocardial strain, strain rate and speckle tracking. Strain and strain rate are novel TDI derived echocardiographic modalities that are now available. Myocardial strain is the deformation of the heart muscle expressed as one dimension. Systolic strain rate measures the rate of deformation of myocardial tissue segment and it represents the deformation between end diastole and end systole. Several studies have shown that strain and strain rate can detect subclinical dysfunction when conventional echocardiography is normal in patients with cardiomyopathy. These techniques have had implication in the early detection and prognosis in Fabry’s disease, cardiac amyloidosis and Fiedrich’s ataxia prior to the development of decreased in ejection fraction and left ventricular hypertrophy or dilation.

Bolivia remains the country with the highest Trypanosoma cruzi infection prevalence, especially in the Chaco ecological zone, where house infestation rates remain high and the majority of rural adults are infected with T. cruzi. Because of the extraordinarily high prevalence of infection, this population will be ideal for assessing associations of early signs of CHD.

We have recently completed a population survey of 1554 residents of 7 communities in the area; 52% overall and 97% of adults older than 30 years had T. cruzi infection. Preliminary data demonstrate that 14% of infected individuals older than 15 years had abnormalities by electrocardiogram (ECG) characteristic of CHD (e.g. left anterior fascicular block and/or right bundle branch block). Among the 150 adults screened by ECG plus echocardiogram to date, at least two have advanced CHD with ACC/AHA class I indication for pacemaker placement.
Methods:

Study Design: The current project is carried out in very poor Guarni indigenous communities near the town of Camiri, Bolivia since May 2011. It comprises an epidemiologic and a serologic surveys that determined the prevalence and demographics of Chagas in the region. A cardiac evaluation and serum biomarker measurement from all infected residents ≥10 years of age and a subset of uninfected residents follows the survey. In this phase, our participation consists of performing cardiac examinations in the population sampled, performing and interpreting electrocardiograms and echocardiograms in the participants enrolled in the study.

Inclusion criteria: Study village residents 10 years or older.

Exclusion criteria: Inability to provide informed consent, inability to undergo venipuncture, ECG or echo. Children younger than 10 years will be excluded from the cardiac evaluation phase of the protocol.

Data collection procedures: As part of the cardiac evaluation phase, we will continue to collect data derived from 12-lead ECG and transthoracic 2-D echocardiograms.

ECG: 12-lead surface ECG’s are currently being performed by recently local physicians in the field. Electronic versions of the tracings are obtained and files saved and read by two independent cardiologists blinded to the participants Chagas serology status.

Echocardiogram: We will follow standard echocardiographic technique methods used in clinical evaluation of Chagas cardiomyopathy. Additionally, we will measure strain and strain rate obtained in a longitudinal, circumferential and radial axis by using an algorithm that calculates spatial differences in tissues velocities between neighboring samples within the myocardium aligned along the Doppler beam. Post-processing techniques will be utilized to distinguish pathological deformation from artifacts and optimize calculations of strain, strain rate and possibly speckle tracking. Two independent cardiologists blinded to the Chagas serology status of the participant will read the studies and disagreements reconciled by a third cardiologist.

Serum Biomarkers: The parent study will measure serum BNP and troponin T levels as part of the serum biomarkers of the CHD. These analyses will be performed by study personnel in Bolivia, using commercially available kits (BNP-32 [human] - Extraction-free EIA Kit, Bachem Americas, Torrence CA; Signosis cTnI Enzyme Immunoassay for quantitative measurement of cardiac-specific troponin I, Signosis Inc, Sunnyvale CA). Aggregates of the results will be provided for the correlation with echo and electrocardiographic parameters.

Analysis: For these analyses, we will examine the means and standard deviations or proportions of demographic variables, baseline cardiovascular risk factors. We will perform correlations between echocardiographic, ECG features, and serum biomarkers. Statistical analyses will be performed with SAS 9.0.
**Plan for dissemination:** The results of the study will be shared with the Brown Cardiology program in the form of a Grand Rounds presentation, and will be submitted for publication in peer reviewed scientific journals.

**Budget and travel expenses:**

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References:

13. Pazin-Filho A, Romano MM, Almeida-Filho OC, Furuta MS, Viviani LF, Schmidt A, Marin-Neto JA, Maciel BC. Minor segmental wall motion abnormalities detected in patients with Chagas' disease have adverse prognostic implications. *Brazilian journal of medical and biological*


